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**Title:** Entangled Lives: Implications of the developmental origins of health and disease (DOHaD) hypothesis for bioarcheology and the life course.

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## ABSTRACT

Epidemiological research since the 1980s has highlighted the consequences of early life adversity, particularly during gestation and early infancy, for adult health (the 'Barker hypothesis'). The fast-evolving field of molecular epigenetics is providing explanatory mechanisms concerning phenotypic plasticity in response to developmental stressors and the accumulation of disease risk throughout life. In addition, there is now evidence for the *heritability* of poor health across generations via epigenetic modifications. This research has the potential to invoke a paradigmatic shift in how we interpret factors such as growth insults and immune response in past skeletal remains. It demonstrates that health cannot be understood in terms of immediate environmental circumstances alone. Furthermore, it requires both a theoretical and practical re-evaluation of disease biographies and the life course more generally. Individual life courses can no longer be regarded as discrete, bounded, life histories, with clearly defined beginning and end points. If socio-economic circumstances can have inter-generational effects, including disease susceptibility and growth stunting, then individual biographies should be viewed as nested or 'embedded' within the lives of others. This commingling of life courses may prove problematic to unravel; nevertheless, this review aims to consider the potential consequences for bioarchaeological interpretations. These include a greater consideration of: the temporal power of human skeletons and a life course approach to past health; infant health and the implications for maternal well-being; and the impact of non-proximate stressors (e.g., early life and ancestral environments) on the presence of health indicators.

The relationship between the environment and phenotypic plasticity has long been a key concept within the discipline of biological anthropology (Roberts, 2012). Franz Boas was one of the earliest proponents of environmental plasticity; highlighted by his famous study of American immigrants, in whom he observed generational changes in cranial indices (Caspari, 2009; Roberts, 2012; Lock, 2013). For some decades, phenotypic plasticity, particularly during the developmental period, has been the focus of a great deal of discussion and debate, particularly within the field of evolutionary and developmental anthropology (Bogin et al., 2007). Phenotypic plasticity is defined as “the ability of an organism to react to an internal or external environmental input with a change in form, state, movement, or rate of activity” (West-Eberhard, 2003, 33). Within bioarcheology, the plasticity of the skeletal form and the ability of the skeleton to retain evidence of environmental exposures (which include culturally-induced exposures) have been central to interpretations of body/society interactions in the past (e.g., Cohen and Armelagos, 1984; Roberts and Manchester, 1995; Larsen, 1997; Buikstra and Beck, 2006).

Over the last decade there has been a growing interest within the medical and social sciences concerning the Developmental Origins of Health and Disease (DOHaD) and the role of epigenetic effects in producing phenotypic variation (Meloni and Testa, 2014). Barker and Osmond’s (1986) spatial epidemiological study in the UK established a connection between infant mortality and cardiovascular disease (CVD), implicating intrauterine deprivation as a risk factor. A wealth of research has since highlighted the link between adversity during fetal development and disease in later life (e.g., diabetes and CVD), providing support for the ‘Barker hypothesis’ (e.g., Hales and Barker, 1992; Barker et al., 1993; Barker et al., 2002; Barker and Lampl, 2013). Subsequent research has demonstrated that the post-natal period, up until early childhood (‘the first 1000 days after conception’), is also important for health in adulthood, with poor care, nutrition, and environmental circumstances, adversely affecting developmental trajectories (Barker, 2012, 186). This research has culminated in what is more widely referred to as the DOHaD hypothesis (Waterland and Michels, 2007), which is now the subject of intense research (Low et al., 2012). As a Government review from the UK highlighted, ‘The foundations for virtually every aspect of human development – physical, intellectual, emotional – are laid in early childhood. What happens in these early years ...has lifelong effects on health and well-being’ (Department of Health, 2010, 94). Early life is now regarded as a particularly sensitive period, when even transient episodes of stress (e.g., infectious disease or malnutrition) may produce effects that persist throughout the life course (Waterland and Michels, 2007; Landecker and Panofsky, 2013).

Recent animal studies have established that epigenetic processes provide an underlying mechanism connecting early life stressors and adult morbidity (Gluckman and Hanson, 2006; Waterland and Michels, 2007; Hochberg et al., 2011). Epigenetic factors are those which alter patterns of gene expression, but not the nucleotide sequences in DNA, with phenotypic repercussions (see, amongst others, Haig's (2012) commentary on the origins and current usage of the term). The field of molecular epigenetics is growing rapidly and studies are subject to considerable 'hype' (Ebrahim, 2012; Relton and Davey Smith, 2012); excitement that has translated into high profile media headlines and publications in journals such as *Science* and *Nature*. It is surprising, therefore, that so far bioarchaeologists have remained remarkably silent on the subject. Current engagement with epigenetics in the discipline of bioarchaeology has traditionally focused on macroscopic, non-metric skeletal variants as a means of studying kinship, population movement and 'biodistance'. Gowland and Thompson (2013) include a discussion of molecular epigenetics in their examination of human identity and identification, but do not explicitly address it in relation to the bioarchaeological record. Klaus (2014, 300) provides a brief discussion of epigenetic factors in his wide-ranging analysis of skeletal stress indicators, but overall concludes that, while they are relevant, we cannot observe them in the bioarchaeological record and thus the subject is rendered 'mute'. However, while disentangling the effects of proximate from early life stressors may be problematic, it does not follow that they should be overlooked entirely. This review aims to provide a timely synthesis of current research on molecular epigenetics and the Developmental Origin of Health and Disease (DOHaD) hypothesis and to explore the theoretical and methodological implications for bioarchaeological analyses. In particular, the need for a more prominent life course perspective and appreciation of the impact of intergenerational adversity when interpreting health stress is highlighted. This review does *not* intend to address emerging studies that seek to examine epigenetic alterations in ancient DNA (e.g., Gokhman et al., 2014). While such studies may have future importance, they are currently novel and peripheral to the majority of bioarchaeological research.

### **What is Molecular Epigenetics?**

'Genes aren't what they used to be...' (Fortun, 2009, 255). Reductionist discourses characterized much of the genetic research in the 1990s. The gene as 'the blueprint for life' has now given way to what has been described as a post-genomic age (Meloni, 2014, 2). Papadopolous (2011, 446) controversially states that: 'The moment of the announcement of the human genome project...was probably one of the last instances of celebration of genetic

reductionism'. The 'demise of the gene' may have been overstated (see Pickersgill et al., 2013 and Meloni and Testa, 2014 for a discussion), but scientists are now heralding the age of the 'epigenome', in which *gene expression* rather than *gene sequence* is garnering most of the attention. Haig (2012) highlights the tenfold increase over the last two decades in the relative frequency of articles with epigenetics in the title. The term was first coined by Waddington (1942) in his paper entitled '*The Epigenotype*' to describe the mechanisms whereby the environment and the genotype interact to produce phenotypic plasticity. Epigenetic processes are integral to determining gene expression, with alterations in the epigenetic regulation of specific genes inducing marked phenotypic change (Verduci et al., 2014). The epigenome is almost the antithesis of the genome: characterised as flexible and responsive to social and environmental change (Meloni, 2014). While reductionist discourse has not been eliminated within the epigenetic paradigm (Lock, 2013; Meloni and Testa 2014), context has played a more prominent interpretive role. As such, epigenetic studies have the potential to inter-link body/society interactions and collapse inter-disciplinary boundaries (Landecker and Panofsky, 2013). Discourse surrounding epigenetics often draws upon the analogy of 'memory', referring to the molecular embedding of social and environmental exposures into the 'memory' of an organism (e.g., Thayer and Kuzawa, 2011; Meloni, 2014). These exposures can result in phenotypic change that can remain stable throughout an individual's life course. Some epigenetic modifications have, however, demonstrated reversibility (Francis *et al.*, 2002; Weaver et al., 2005). Epigenetic modifications occur via a number of different mechanisms, but one of the most heavily researched is DNA methylation, which refers to the addition of a chemical compound called a methyl group to a DNA base (Pickersgill et al., 2013, 430). DNA methylation has been described as the '*prima donna*' of epigenetic research and abnormal patterns of methylation have been linked to numerous disease processes (Landecker and Panofsky, 2013, 338). The impact of a variety of social and environmental factors for patterns of methylation has been explored, including parental diet (e.g., Ng et al., 2010), infant care (e.g., Weaver et al., 2004; Meaney and Szyf, 2005), child abuse (e.g., McGowan et al., 2009) and social status (e.g., Borghol et al., 2012), to name but a few. However, there are currently many unknowns regarding the implications of DNA methylation, along with other epigenetic markers, for the phenotype (Heijmans and Mill, 2012; Pickersgill et al., 2013; Meloni and Testa, 2014). Epigenetic research is still in its fledgling stages and, while it is burgeoning, it is described as: 'not a given set of facts but an active field of open questions and contestation...' (Landecker and Panofsky, 2013, 336). Nevertheless, some startling results are beginning to emerge with implications concerning the interplay between the body, society and health as well as the DOHaD hypothesis. Epigenetic processes are fundamental to developmental plasticity, allowing phenotypic flexibility in response to diverse environmental circumstances

(Kuzawa and Bragg, 2012). The relevance of the DOHaD hypothesis and epigenetic mechanisms for bioarcheology will be explored below.

### **Early Life Adversity**

The effects of under- and malnutrition at different gestational ages has been linked to different birth phenotypes, resulting in a variety of metabolic problems in later life (Barker et al., 1993; Waterland and Michels, 2007). Studies of humans exposed, through natural circumstances, to challenging environmental conditions have proven insightful in terms of the DOHaD hypothesis (Uauy et al., 2011). A particularly well-known and often cited example is the Dutch Hunger Winter of 1944-45. During this five-month period, food rations in the Netherlands plummeted to under a 1000 Kilocalories per person per day, resulting in a well-documented, discrete famine event. Longitudinal studies have identified increased propensities for metabolic and psychiatric disorders in those individuals who were developing *in utero* during this time (Roseboom et al., 2001). Epigenetic changes to gene expression occurred during fetal development as an adaptive response to sub-optimal conditions (Heijmans et al., 2008; Landecker, 2011, 177). In the Dutch famine, food supplies soon returned to normal, thus creating a 'mismatch' between the starvation-level intrauterine signals and adequate post-natal nutrition (Gluckman et al., 2011, 13); essentially resulting in maladaptation and leading to greater chronic disease susceptibility in later life (Uauy et al., 2011). Subsequent additional longitudinal and retrospective human population studies discovered that, in addition to *in utero* development, infancy and early childhood growth tempo also plays a significant role in later life well-being (Barker et al., 2001, 2011; Eriksson et al., 2001).

Current epidemiological investigations in support of DOHaD have tended to focus on the impact of early life adversity for *chronic* disease risk, such as diabetes or cardiovascular disease. However, prior to the epidemiological transition (late 19<sup>th</sup>-early 20<sup>th</sup> centuries), infectious rather than chronic diseases were a more prominent cause of death (Mercer, 2014). It could be argued, therefore, that early life adversity is of less relevance to archaeological contexts, given the lower life expectancy and comparatively minor role of chronic disease in past population morbidity and mortality. However, early life nutritional stress has also been shown to have implications for the immune response. For example, studies of health in rural Gambia have shown that children born shortly after the 'hungry season' suffer from an increased risk in mortality from infectious disease in early adulthood (Moore et al., 1999; 2004). The authors argue that immune function and disease susceptibility is 'programmed' in early life and affected by intra-uterine growth retardation. Additionally, studies of infant mortality and birth weight in Gambia have shown that infants

conceived during the hungry season have higher levels of methylation at a number of loci with phenotypic repercussions (Waterland et al., 2010; Dominiguez-Salas et al., 2014). McDade (2002, 2012) has likewise highlighted the detrimental effects of pre- and post-natal childhood nutritional deficiencies for immune responses in later life. These studies emphasize the plasticity of the human immune function and development up until early childhood (Barker, 2012).

The link between early life stress and later life morbidity and mortality can be investigated in the bioarchaeological record. Skeletal evidence can be used to construct osteobiographies of health due to the known chronological parameters of the developing bones and teeth (Robb, 2002; Sofaer, 2006). The use of different skeletal growth parameters may reveal age-specific growth disruption patterns that can be correlated with social constructions of the life course, such as weaning, or the commencement of labour outside of the home (Newman and Gowland, 2015). Life course events such as these during the childhood period can result in increased exposure to pathogens; however, the immune response is energetically costly and an elevated inflammatory response has been linked with life-history trade-offs, resulting in growth stunting (McDade, 2003, 2008).

Limb length has been shown to be more 'plastic' than trunk height in relation to environmental stressors (e.g., Wadsworth et al., 2002); however, differences in vertebral dimensions between archaeological populations have also been correlated with age-at-death (Watts, 2013). The transverse and anteroposterior diameters of the neural canal are 'locked-in' by five years of age, providing an indicator of early post-natal growth, while vertebral body height may continue growing into early adulthood. Therefore, the complementary use of these parameters can be used to construct an osteobiography of growth stunting in early childhood, with implications for adult morbidity (Newman and Gowland, 2015). Pomeroy and colleagues (2012) also discuss the disproportionate effects of environmental stressors on body proportions in their study of living children from highland and lowland Peru. Here, the ulna and tibia were found to be most sensitive to stressors such as poor nutrition. While not conducted on a skeletal assemblage, Pomeroy et al.'s (2012) study would translate well to archaeological data-sets in order to investigate correlations between stressors, relative limb segment length, and age-at-death in the past. While growth stunting may be conceptualised in terms of a life-history trade-off, it has significant adverse short and long-term health consequences, such as increased susceptibility to infectious disease (Pelletier, 2000; McDade, 2003; 2012) and impaired cognition (Chávez, 2000; Uauy et al., 2011).

Malnutrition has been highlighted as a particularly significant factor in the DOHaD hypothesis. Within bioarcheology, recent advances in the analysis of high resolution isotopic



data from dentine can be used to 'map' longitudinal dietary changes during infancy and childhood (e.g., Beaumont et al., 2012, 2013, 2015). Nitrogen and carbon isotope values can be plotted at intervals of less than one year, from just before birth to approximately fifteen years of age, depending on the tooth being sampled (Montgomery et al., 2013). When integrated with the skeletal evidence for growth, the impact of childhood nutrition and health on adult morbidity and mortality can be observed. Such techniques provide high resolution comparative data for the period in which the tooth was forming in children who died as well as those who survived to adulthood (e.g., Beaumont et al., 2013). In addition to providing information relevant to the DOHaD hypothesis, this type of analysis could also help to address the osteological paradox (Wood et al., 1992), because these parameters allow a comparison of health insults and diet between survivors and non-survivors.

Recent paleopathological studies have provided support for the 'Barker hypothesis' within archaeological contexts, noting correlations between childhood indicators of health stress, such as enamel hypoplasia and growth stunting, and reduced adult longevity (e.g., Armelagos et al., 2009; Watts, 2011, 2013). As discussed above, the DOHaD hypothesis has led to a greater clinical focus on early life in terms of medical intervention to mitigate against future health risks. Within bioarcheology there has been a greater focus on childhood health over recent years (e.g., Lewis, 2007), although this has yet to be considered in detail in terms of the DOHaD hypothesis, or intergenerational health. The latter will be explored further below.

## **Mom's the Word**

Given the findings of research into the DOHaD hypothesis and the emphasis on early life, the mother/infant nexus has become the subject of intense scrutiny (Richardson et al., 2014). Epigenetic mechanisms underlying this phenotypic variation have been explored primarily through laboratory experiments on rodents. Scientists have examined the effects of a range of variables, including maternal nutrition and psycho-social stressors, on the offspring epigenome and health (Francis et al., 2002). As discussed above, fetal development has been established as a period of sensitivity to epigenetic plasticity. Subsequent epigenetic effects have been shown to have lifelong consequences through their stable propagation during mitotic cell division (Hochberg et al., 2011). As Hochberg and colleagues state (2011, 194): "Abnormal maternal behavior, inadequate maternal feeding, and exposure to deleterious environmental compounds during critical periods of life (periconception and fetal and infant development) can change developmental trajectories."

The significance of the human intrauterine environment for life-long health outcomes has rendered this nine-month window a target for early medical intervention (Pickersgill et al., 2013). The role of the mother within this paradigm has been re-imagined from that of an environmental ‘buffer’ – nurturing and protecting the infant from harmful external exposures – to that of a ‘vector’ – a potential source of long-term toxicity for the developing infant (Richardson et al., 2014). The expectant mother has become culpable and her behaviour subject to greater censure under both the medical and public gaze (Richardson et al., 2014). The logic is that by optimising maternal health during this gestational period, the lifelong health of the developing offspring will be secured. However, a recent article in *Nature*, rallied against this reconceptualization of the maternal body, appealing ‘don’t blame the mothers’ (Richardson et al., 2014). In actuality, research has shown that targeting this nine-month gestational window is unlikely to be the answer for optimizing future health (Chung and Kuzawa, 2014). Instead, the socio-economic circumstances of the mother during her *own* childhood has proven highly significant for parameters of health relating to her offspring (Barker, 2012). For example, Sletner and colleagues’ (2014) clinical study of socio-economic life history and the size and body composition of offspring, demonstrated that mothers who had experienced a relatively impoverished childhood would have neonates with less optimum growth parameters, irrespective of current socio-economic position. These findings build upon other studies that have highlighted the inter-generational effects of the mother’s nutritional life history (e.g. Chung and Kuzawa, 2014).

Infant skeletal remains provide archeologists with important information regarding past infant care, but additionally shine a spotlight on the ‘invisible’ mother, even in the absence of a demonstrable connection in the archeological record (e.g. mother/infant burials). Pathological lesions observed on infant bones provide important proxies for the study of past maternal health. The developing fetus is prioritised by the pregnant body in times of nutritional stress, with resources diverted to support the needs of the infant; therefore nutritional deficiencies in the fetus/infant reflect the very poor health status of their mothers (Chávez et al., 2000). Isotopic analysis of infant remains can also be particularly informative in this regard. Beaumont et al. (2015) have noted a disparity between maternal  $\delta^{15}\text{N}$  values and perinatal off-spring, with the latter often elevated. This difference occurs because the perinatal values reflect the period of development *in utero*, whilst bulk values relating to adult females represent data relating to the last 5-10 years of life (depending on the bone sampled). Elevated  $\delta^{15}\text{N}$  values in archaeological infants have traditionally been interpreted as providing a breastfeeding signal. However, Beaumont and colleagues (2015) argue that, for perinates, the high nitrogen values may reflect poor

maternal health. If the mother is ill or malnourished, her body will recycle proteins and this similarly leads to higher nitrogen values, potentially mimicking a breastfeeding signal (Beaumont et al., 2015). The association between high  $\delta^{15}\text{N}$  values and starvation has also been recorded in the clinical literature in studies of hair samples obtained from individuals attending clinics for eating disorders (e.g., Mekota and Grupe, 2006). The infant, therefore, provides high resolution *maternal* isotope values, in the absence of the mother herself. These values could therefore be examined in relation to more traditional paleopathological indicators of poor health (e.g., delayed growth, enamel hypoplasia, cribra orbitalia) in order to examine maternal health. Contrary to the argument that archeological cemetery data is limited due to the cross-sectionality of the data (Klaus, 2014), it does in fact exert clear temporal power, providing life course and intergenerational information on health.

Another example of the linked well-being of the mother and infant is discussed by Kuzawa and Quinn (2009) in relation to adult stature. Stature is one of the most common anthropological calculations and is often used as a general indicator of population well-being (Steckel, 2009). Poor nutrition most profoundly influences adult stature during fetal, infant and early childhood development – the period of life during which food is predominantly sourced from the maternal body, via the placenta, or breastmilk (Kuzawa and Quinn 2009). For example, a longitudinal study by Chávez and colleagues (2000) showed a clear decline in breast milk consumption by the infants of poorly nourished mothers by two to three months of age, contributing to early childhood malnutrition and poorer growth. Studies of growth stunting in developing countries have shown that faltering occurs early in life and is most pronounced by two years of age (Kuzawa and Quinn, 2009). These height deficits at two years tend to be maintained into adulthood. Thus, adult size is mostly closely linked to matrilineal nutritional well-being and history (Kuzawa and Quinn, 2009).

Interpretations of growth stunting in young infants from archaeological contexts should therefore be considered in terms of maternal health. Women who are under-nourished prior to and during pregnancy are more likely to present intrauterine growth restriction. Sibley et al.'s (1992) study of pelvic size amongst females from a medieval population in Sudanese Nubia found a high proportion of individuals with contracted pelvises. In this study, a link was made between evidence for growth retardation in the mother and neonatal/maternal morbidity and mortality. From a life course perspective, growth stunting of the mother as a consequence of her own poor childhood environment resulted in the poor health of her offspring, thus perpetuating the cycle of deprivation (Uauy et al., 2011). Other factors relating to maternal health, such as obesity and vitamin D status have also been

linked to increased risks of osteoporosis and bone fractures in offspring in later life (Delgado-Calle et al., 2012; Holroyd et al., 2012)

As discussed above, the post-natal and early childhood biocultural environment is also a period in which adverse environments can have life-long consequences for health. Murine studies have demonstrated that differences in maternal care in early infancy can have consequences for epigenetic processes which help regulate adult stress reactivity (Weaver et al., 2004). These findings have been echoed in human studies of suicide victims with a history of childhood abuse. These individuals exhibited epigenetic changes to their hippocampal glucocorticoid receptor when compared to suicide victims without a history of abuse and a control group (McGowan et al., 2009).

Aspects of post-natal care, such as breastfeeding and duration, or the use of artificial formula, may also have life-long health consequences for health. Through the medium of breast-milk the infant will inherit the mother's immunologic life history (McDade, 2003). In marginal environments, with poor hygiene and nutrition, infants breast-fed for only a short duration will have higher rates of infectious morbidity than those who are breast-fed for longer (McDade, 2003). The link between breast-feeding and improved neural-behavioural development, growth, and reduced infection has been evidenced in numerous clinical studies (American Academy of Pediatrics, 2012). Formula feeding has also been associated with disturbed metabolic regulation and obesity in later life (Verduci et al., 2014). While breastfeeding duration is often conceptualised in negative terms (i.e. energetic burden) for the mother (McDade, 2003), breastfeeding is also beneficial to maternal health, including reduced risk of breast and ovarian cancer, cardiovascular disease and autoimmune diseases such as rheumatoid arthritis (American Academy of Pediatrics, 2012). The positive benefits of breastfeeding, for both mother and infant, endure beyond its duration and can have life-long benefits.

To date, there has been little written on pregnancy or motherhood based on skeletal samples from archaeological sites. However, the use of skeletal evidence within a DOHaD framework facilitates a bioarcheology of motherhood. Recent studies that seek to examine puberty and menarche from the archaeological record are also relevant here (Shapland and Lewis, 2013). Within the bioarcheological record, the infant may be used as a proxy for the mother, but they are also connected in terms of their biocultural biographies and epigenetic inheritance and this will be explored further below.

## **Inheriting Well-being**

The inheritance of the effects of adverse environmental or social conditions from grandmother to grandchild has been established and discussed within the framework of DOHaD and epigenetic inheritance (Gluckman et al., 2011; Davey Smith, 2011, 2012; Barker, 2012; Sletner et al., 2014). For example, longitudinal studies of the Dutch famine victims showed that three generations were *directly* affected by the famine – the expectant mother, her offspring, and her grandchildren; the latter because the ova develop in the fetus during gestation (Barker, 2012). As a consequence, an individual's phenotype will be the 'result of lifelong remodeling of the epigenome due to a complex interaction between the genotype and the *ancestral* and current environments' (Hochberg et al., 2011; 194, my emphasis). The significance of this intergenerational inheritance is particularly profound in terms of current conceptualizations of the life course. An individual's physical and social world in early life can shape, not only their own biological processes (including health) during their lifetime, but also those of their children and grandchildren (Thayer and Kuzawa, 2011; Rando, 2012).

This research is significant for bioarcheological interpretations because it extends relevant biocultural circumstances back to events prior to conception. Studies report that 'the environment experienced by parents can affect offspring who never experienced that environment' (Rando, 2012, 703). Food availability for paternal as well as maternal grandparents has been linked to cardiovascular diseases two generations later, likely via epigenetic mechanisms (Kaati et al., 2002). Such factors also contribute to the heterogeneity of individual responses to similar environmental exposures, because this response is governed, in part, by ancestral experiences (Sletner *et al.*, 2014, 448). Therefore, poor health arises as a consequence of the accumulation of risk, potentially across generations, rather than a single life course (Davey Smith, 2011). When interpreting health from past skeletal remains, the concept of 'linked lives', as well as cumulative biographies should be considered. For example, if one takes the example of poor growth in childhood (discussed above), parental exposures during their own childhood are known to be significant factors (Sletner et al., 2014). This has important implications for our interpretation of paleopathological lesions and stunted growth in the bioarcheological record, where the tendency has been to consider immediate causalities alone. This also raises the question of how to tease out inherited from proximate forces in archeological cemetery evidence (see below). The construction of adequate osteobiographical data from skeletal assemblages through the use of parameters that can assess growth and health at different stages of the life course, integrated with high resolution isotope data, would be helpful in this regard. Such analyses on a cemetery-wide scale tend not to be undertaken given that the isotope technology is new, but may become a more realistic prospect in the future. However, even

should intergenerational effects prove impossible to isolate, it does not follow that this factor should be disregarded: if ancestral adversity exerts an effect on health, then it should be considered in interpretations. The commonly assessed skeletal indicators of poor health analysed in bioarcheology (e.g. cribra orbitalia, enamel hypoplasia, growth disruption) are regarded as 'non-specific' because of their multiple and overlapping etiologies. The immediate environment is certainly a prominent factor with regard to their prevalence. However, generational adversity has also proven to be a cause of growth disruption and infectious disease susceptibility, particularly in marginal circumstances (e.g., Waterland et al., 2010; Hochberg et al., 2011, 181; Dominiguez-Salas et al., 2014). For example, the study by Sibley and colleagues (1993) highlighted the inter-generational impact of poor nutrition on female pelvic dimensions. These females were likely to have given birth to infants who were small for gestational age, a factor linked to a variety of elevated health risks (Barker, 2012). Chung and Kuzawa's (2014) study of pregnant females in the Philippines, highlighted a correlation between maternal leg length and the birth weight of their infants. The leg length of these females was related to nutritional status during their own growth and thus the study likewise highlighted inter-generational effects of the mother's own childhood nutrition on the health of her offspring. A clearer understanding and integration of archeological context with skeletal evidence, in addition to osteobiographical data, should help to facilitate a proximate versus DOHaD assessment, though the two will be problematic to disentangle.

Food insecurity is likely to have been a feature of many societies in the past, whether related to seasonal fluctuations in available resources, disease epidemics, or famine events and these may also have inter-generational health implications. As the Dutch Famine example highlights, even short term exposure to malnutrition can have generational impacts on health. In past populations subjected to episodic famine, one would expect a range of health and physical consequences in those directly affected. However, the physiological impact of a single famine episode has the potential to reverberate well beyond the immediate time-frame of the event itself. This potentially introduces a 'time-lag' into the skeletal record, when the physiological expression of poor health may endure beyond the chronology of a particular catastrophe. Jasienska (2009) and Kuzawa and Sweet (2009) invoke epigenetic inheritance as a means of explaining the consistently higher levels of infant mortality and cardiovascular disease amongst contemporary African Americans when compared to European Americans of equivalent socio-economic position. Poor infant health, it is argued, cannot solely be explained by proximate nutrition and disease load, but instead is interpreted to be a consequence of social structures endured by an infant's ancestors. It is suggested that the impact of generations of slavery, along with continuing psycho-social

stresses as a consequence of racist ideologies and social inequalities continue to exert a toll on health. As Gravlee (2009) has stated, such causalities, demonstrate the way in which the social construction of race can become biologically embedded, with detrimental effects for health, including cardio-vascular disease and infant mortality.

Within the field of molecular epigenetics, transgenerational inheritance, the transmission of epigenetic traits to *great*-grandchildren, is much more controversial (Kaiser, 2014; Davey Smith, 2012; Ebrahim, 2012; Low et al., 2012). This should be distinguished from the aforementioned intergenerational impacts. Instead it is used to describe epigenetic effects that persist in those generations not directly exposed to the initial trigger (Heard and Martienssen, 2014). Transgenerational epigenetic processes involve the inheritance of epigenetic traits across the germ-line, which is commonly observed in plants and other multicellular organisms (Rando, 2012; Keiser, 2014). In mammals, germ-line 'reprogramming' occurs early in embryo development and this process is thought to 'wipe clean' the effects of any epigenetic alterations (Heard and Martienssen, 2014). However, recent experiments with rodents have challenged this, finding that aspects of health such as chronic social instability can cause enhanced anxiety and behavioral alterations in *three* generations of offspring, with DNA methylation being retained in the germ-line (Franklin et al., 2010; Saavedra-Rodriguez and Feig, 2013). Studies of DNA methylation in mice have found that some loci do in fact escape the reprogramming process and thus provide possible candidates for mammalian transgenerational inheritance (Heard and Martienssen, 2014, 103). Further research into this phenomenon is currently being conducted through paternal lineages (e.g., Radford et al., 2014). However, for the moment, transgenerational inheritance of epigenetic effects through the germ-line remains controversial in small mammals, let alone human populations (Kaiser, 2014). Nevertheless, the intergenerational effects of adverse circumstances such as poor nutrition and other environmental exposures have provided firm evidence of direct impacts on offspring and grand-offspring health (e.g. Sletner et al., 2014). Studies have demonstrated the repercussions of socially induced exposure, long after events have passed, emphasizing the need for a life course and intergenerational approach to health. Archeological context is also vital when interpreting this evidence; comparisons between high and low status groups, particularly amongst populations with known poor social mobility (e.g., post-medieval England) could prove fruitful (Klaus, 2014). Indeed social status has been the focus of intensive epigenetic research in contemporary populations and is regarded as one of the strongest social determinants of health.

## **Health and the Social Gradient**

The consequences of epigenetic processes and the DOHaD can be observed at a number of levels in society, but perhaps most starkly by the gradient of ill health woven into the social strata, with those at the top of the social ladder experiencing much better health than those at the bottom (Wilkinson, 2006; Hertzman, 2012). Overall health is poorer in societies that are less equal, with the very poorest individuals experiencing elevated risks with respect to a wide range of common diseases (Wilkinson, 2006; Thayer and Kuzawa, 2011). There is currently a large body of empirical data that provides evidence for the social gradient of health and this has been supported more recently by studies of DNA methylation (see Hertzman, 2012 for a review). For example, the longitudinal British Birth Cohort study has followed a large sample of individuals from their birth in 1958 to the present day. Recent analysis of blood samples has shown that socio-economic position in early life corresponds with differential levels of methylation during adulthood (Borghol et al., 2012). Individuals of low socio-economic position within this cohort generally had poorer physical, emotional and cognitive status (*ibid.*). Likewise a study of DNA methylation between the poorest and most affluent areas of Glasgow found a link between lower levels of methylation and the poorer communities, which in turn demonstrated enhanced disease risk (McGuinness et al., 2012).

Status and inequality have been studied within bioarchaeology (e.g., Robb et al., 2001; Sullivan, 2005; Redfern and DeWitte, 2011; DeWitte et al., 2015), but arguably not to the same extent as other aspects of social identity such as gender (e.g., Grauer and Stuart-Macadam, 1998; Sofaer, 2006; Holliman, 2011) and age (e.g., Lewis, 2007; Agarwal and Beauchesne, 2011). Only rarely have paleopathological studies of status integrated current medical and theoretical thought concerning the impact of psycho-social stressors and DOHaD (e.g., Armelagos, 2009; DeWitte et al., 2015; Gowland and Newman, in press). It is worthwhile considering the archeological evidence for social inequalities in past societies and the potential health effects of these material and psycho-social disparities. For example, with the Roman occupation of Britain in AD 43-410, the indigenous population was largely assimilated into the structured hierarchy of the Empire. While there were many material and technological benefits to being part of the Roman Empire, the skeletal evidence reveals a decrease in stature and an overall increase in non-specific indicators of health stress (e.g., Roberts and Cox, 1993; Gowland and Redfern, 2010; Redfern and DeWitte, 2011). A similar skeletal pattern has been observed elsewhere in the Roman Empire (e.g., Gianecchini and Moggi-Cecchi 2008). This evidence may be regarded as counter to the apparent increase in material wealth during this period. However, one explanation for this dip in health is the imposition of an increasingly hierarchical structure on the local populace, resulting in greater social inequalities and increased psycho-social stresses. Paleopathologists should be mindful of the fact that social identities such as poverty and inequality may carry with them a



heritable phenotypic legacy. These serve to create phenotypic disadvantage that interacts synergistically with social environment to become mutually reinforcing, particularly in societies with low social mobility (Chávez et al., 2000).

Cross-sectional and longitudinal stature data have often been utilised as useful proxies for socio-economic environment in populations studies (Steckel, 2009). However, final adult height can mask a variety of childhood experiences. For example, Barker and colleagues' (2011) study of the Helsinki birth cohort demonstrated that boys who were tall when they entered school (indicative of adequate nutrition and environment) had a longer life-span. However, those boys who were tall as a consequence of rapid catch-up growth after a period of stunting had shorter life-spans. Bioarchaeologists have the potential, not just to access adult stature in a cross-sectional sense, but to assess how that stature was achieved through the analysis of a variety of skeletal parameters relevant to different life course stages. For example, analysis of the body proportions of adults and children, with special attention to the proportional lengths of the distal limb segments will be suggestive of environmental stressors (Pomeroy et al., 2012; Chung and Kuzawa, 2014). The effects of growth stunting on individual long bone lengths may be masked by catch-up growth, however, the analysis of skeletal parameters that fuse earlier in life can provide additional information regarding early childhood (e.g., transverse diameter of the neural arch; Watts, 2013; Newman and Gowland, 2015). Evidence for compensatory growth can then be compiled (e.g. small transverse diameter/ distal limb segment, but average adult stature) and correlated with mortality risk. This information can be assessed in relation to the presence of childhood indicators of poor health (e.g., cribra orbitalia), with a particular focus on the age of onset of these lesions within the skeletal sample (Walker et al., 2009). All of these data should then be integrated with longitudinal dietary data obtained from incremental isotope analysis of dentine. The relationship between paleopathological lesions and dietary isotope ratios can be 'mapped'. High resolution isotope analysis of teeth can also be examined for periods of starvation (i.e. elevated nitrogen values) in both the adult survivors and the non-survivors who died in childhood (Beaumont et al., 2013, 2015; Montgomery et al., 2013). Growth deficits in survivors, whose isotope evidence also indicated a period of deprivation, would be of particular interest for correlating with other skeletal parameters of growth stunting. The age at which growth deficits and paleopathological lesions begin to occur is crucial to interpretations, in particular regarding the likely origin of these as inherited rather than proximate. Currently, there is a tendency to interpret such lesions in the skeletal remains of infants and young children in terms of breastfeeding practices or child care alone, but the inheritance of poor health may be assessed through the parameters discussed above. If female growth within a cemetery was compromised during early childhood, then

growth deficits and paleopathological lesions observed in infants and children should also be considered in terms of an epigenetic legacy, including compromised immune response, rather than weaning timetable alone (Chung and Kuzawa, 2014). It is important to also assess fetal growth parameters as these are known to be affected by poor peri-conception health (Heijmans et al., 2008; Barker, 2012).

In the archeological record, we often encounter migrant groups and isotopic information on migrant status will also be beneficial to interpretations. Studies of living populations have shown health disparities in the offspring of migrants from poorer countries, when compared to their indigenous counterparts, even when present socio-economic position is equivalent (e.g. Sletner et al., 2014). Presumably this effect would work in reverse in those migrants travelling from well-off to impoverished environmental circumstances. In the latter case, one might expect the first generation of offspring to be relatively buffered against harsh environments by the better health status of their parents. This resilience would then be expected to diminish over subsequent generations if conditions remain poor. Migrant status can include within-country migration to contrasting environments, such as from rural to urban environments (e.g., during the industrial revolution in the UK). Through the above analyses, relationship between health insults and mortality in later life can be accessed, providing an archaeological perspective on the DOHaD hypothesis and the inheritance of poor health.

## **The Body and Society in Bioarcheology**

Over recent years there has been a move towards a 'social bioarcheology': the integration of social theory with the analysis of human skeletal remains (e.g., Gowland and Knüsel, 2006; Sofaer, 2006; Knudson and Stojanowki, 2008; Agarwal and Glencross, 2011). This theoretical move has evolved out of the biocultural approach to skeletal remains, but has also been informed by research on the body and society from across the social sciences and philosophy (Gowland and Thompson, 2013). Now, research into epigenetics and DOHaD have provided important contributions to these debates, demonstrating a mechanism whereby the social and biological sciences can be more completely reconciled (Landecker and Panofsky, 2013). As Guthman and Mansfield highlight (2013, 497) "there is nothing about the body that forms a solid boundary – or threshold – between it and the external environment". Further, epigenetic research demonstrates that ancestral psycho-social and biological experiences (e.g. past anxieties, dietary practices, relationships and so forth) exert an active force on health (Landecker and Panofsky, 2013). While a life course approach to health is increasingly feasible within bioarcheology, the inheritance of poor

health raises deeper philosophical questions concerning the current Western conceptualisation of the life course as discrete and bounded (Niewohner, 2011). If social and physical factors affecting our grandparents have consequences for our own gene expression, with attendant consequences for mental and physical well-being, then when does our biography begin and theirs end? The moment of birth, or even conception, within this paradigm, seems relatively arbitrary (Gowland and Newman, in press). The current life course paradigm adopted within bioarchaeology (i.e. discrete, linear, and individualized), is no longer congruent with current DOHaD and epigenetic models in which adverse biocultural effects are transmitted between generations. A more appropriate analogy may be that of 'Russian Dolls': our life courses are 'nested' and entangled, both socially and biologically, across several generations. Niewohner (2011, 289-290) refers to the 'embedded body' as one 'that is heavily impregnated by its own past and by the social and material environment within which it dwells. It is a body that is imprinted by evolutionary and transgenerational time, by early-life and a body that is highly susceptible to changes in its social and material environment'. Niewohner (2011, 290) also notes the contrast between this embedded body and that of the autonomic, bounded individual, urging anthropologists to think more creatively about the human body. Innovative interpretations of the bioarchaeological evidence should now seek to take into consideration the lamination and accumulation of multiple environmental and social exposures over several generations. People are not biologically disparate, but commingled: bodies within bodies.

## **Conclusion**

Interpreting pathological lesions from skeletal remains can be a complex endeavor; often confounded by the non-specific nature of many skeletal lesions, multiple and overlapping etiologies, and the paradoxical nature of the data (Wood et al., 1992; Ortner, 2003). The addition of early life risks and intergenerational effects, serves to further 'muddy the waters'. This is an emerging field of research and there are currently many unknowns regarding the skeletal manifestation of DOHaD and epigenetics. However, if such factors are contributing to the disease-scape of past skeletal populations – and contemporary evidence suggests that they must be – they cannot be disregarded. Indeed epigenetics has been described as being 'at the heart of phenotypic variation in health and disease' (Feinberg, 2007, 438). Epigenetics and DOHaD provide an important mechanism for understanding the relationship between society and health in the past as well as the present. Research in these fields are serving to collapse of the mind/body divide that has structured Western knowledge for the past few centuries. It reinforces the connectivity between individuals genetically,

epigenetically, physiologically and socially. In order to examine these factors in past populations, both cemetery-wide samples and individual osteobiographical approaches should be used in conjunction. The above review has highlighted the following key points and recommendations for bioarcheology:

- 1) Infants can no longer be regarded as at the periphery of the human experience. They are central to the construction of past population health and bioarcheological research should seek to reflect this through a greater focus on fetal and infant metric and paleopathological indicators of health stress.
- 2) DOHaD research emphasises the entangled fortunes of the mother/infant nexus, allowing the latter to act as a proxy for the former, and facilitating a bioarcheology of pregnancy and motherhood. Health *can* be accessed on a generational scale, despite the perceived cross-sectionality of archeological cemetery evidence.
- 3) A life course approach to health is now regarded as crucial in the medical sciences and bioarcheology should seek to embrace this approach more explicitly in studies of past health. The temporal quality of the skeleton lends itself to such a project. High resolution isotope data should be integrated with data from a range of growth parameters and paleopathological data, to identify adults who endured childhood stress and to differentiate children who died following sustained periods of poor health from those who were 'healthy' prior to death. Age of on-set of factors such as growth stunting and active paleopathological lesions are crucial to interpretations concerning causalities (e.g., stunting prior to three years is likely to relate to maternal health).
- 4) Epigenetics raises deeper challenges regarding current conceptualizations of the beginnings and end of life, as well as the notion that individuals have discrete and separate biographies. At no point in time is the human body a *tabula rasa*; instead the biological tissues of the body are saturated by the social exposures of our early life and ancestral environments (Gowland and Thompson, 2013).
- 5) Social factors such as inequality can produce heritable disadvantages for well-being in terms of immune status, or susceptibility to chronic disease, that then serve to perpetuate the status quo. Paleopathological analyses could benefit from a closer engagement with current literature on the social gradient of health.
- 6) Past environmental catastrophes or periods of social upheaval may have health consequences generations after the event, while seasonal variation in resources amongst some populations can result in stark heterogeneity in mortality risks.

As a final comment, within bioarcheological interpretations, it is worth considering Budgeon's (2003, 50) prescient observation that bodies should be reconceptualised as '*events*' that are

continually in the process of becoming – as multiplicities that are never just found but are made and remade’.

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